Epidemiological aspects of pleural tuberculosis in the state of São Paulo, Brazil (1998–2005)*

Aspectos epidemiológicos da tuberculose pleural no estado de São Paulo (1998-2005)*

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Abstract

Objective: To analyze the epidemiological characteristics of and trends regarding the incidence of pleural TB.

Methods: This was a retrospective descriptive study of TB cases reported between 1998 and 2005 and compiled from the Epidemiological Surveillance Tuberculosis System (Epi-TB database). Results: A total of 144,347 new cases of TB were reported during the period studied. Pulmonary TB was the predominant form (118,575 cases; 82.2%). Among the extrapulmonary forms (25,773 cases; 17.8%), pleural TB was the form most often reported (12,545 cases; 48.7%). For all forms, the incidence (per 100,000 population) decreased (from 49.7 in 1998 to 44.6 in 2005; R² = 0.898; p < 0.001), whereas the incidence of pleural TB remained stable (4.1 in 1998 and 3.8 in 2005; R² = 0.433; p = 0.076). The highest incidence of pleural TB was found among males (2:1) aged from 30 to 59 years. Of the 12,545 patients with pleural TB, 4,018 (32.0%) presented comorbidities: alcoholism (9.5%); HIV (8.0%); diabetes (3.3%); and mental illness (1.2%). The diagnosis was based on bacteriological (14.2%) and histological (30.2%) methods, as well as on unspecified methods (55.6%). Conclusions: Pleural TB was the predominant extrapulmonary form of TB in the state of São Paulo, with a stable incidence between 1998 and 2005, although there was a trend toward a decrease in the incidence of the pulmonary forms. The diagnosis of pleural TB was confirmed through histology and bacteriology in 44.4% of the cases.

Keywords: Pleural effusion; Tuberculosis, pleural; HIV.

Resumo

Objetivo: Analisar as características epidemiológicas e tendências quanto à incidência de TB pleural. Métodos: Estudo descritivo, retrospectivo dos casos de TB reportados entre 1998 e 2005 e coletados do banco de dados do Sistema de Notificação de Tuberculose (Epi-TB) da Secretaria de Saúde do Estado de São Paulo. Resultados: Foram notificados 144.347 casos novos de TB durante o período estudado. A forma pulmonar foi predominante (118.575 casos; 82,2%). Das formas extrapulmonares (25.773 casos; 17,8%), a pleural foi a mais referida (12.545 casos; 48,7%). A incidência (por 100.000 habitantes) de todas as formas diminuiu, (49,7 em 1998 e 44,6 em 2005; R² = 0,898; p < 0,001), enquanto a incidência de TB pleural permaneceu estável (4,1 em 1998 e 3,8 em 2005; R² = 0,433; p = 0,076). A maior incidência de TB pleural ocorreu em pacientes do sexo masculino (2:1) entre 30 e 59 anos de idade. Dos 12.545 pacientes com TB pleural, 4,018 (32.0%) apresentaram comorbididades: alcoolismo (9,5%); HIV (8,0%); diabetes (3,3%); e doença mental (1,2%). O diagnóstico referido fundamentou-se em métodos bacteriológicos (14,2%) e histológicos (30,2%), assim como outros não especificados (55,6%). Conclusões: No estado de São Paulo, a TB pleural foi a forma extrapulmonar predominante, apresentando incidência estável no período entre 1998 e 2005, apesar da tendência de diminuição das formas pulmonares. A histologia e a bacteriologia definiram o diagnóstico em 44,4% dos casos.

Descritores: Derrame pleural; Tuberculose pleural; HIV.
Introduction

According to the World Health Organization, TB is the leading cause of death among infectious diseases. In 2005, Brazil ranked 15th among the 22 countries with the heaviest TB burden (60 new cases per 100,000 population). This number contrasts with the incidence reported by the Brazilian National Ministry of Health (41/100,000 population), suggesting the existence of a considerable number of unreported cases. Trends that have been observed for at least two decades demonstrate that TB cases are concentrated in capital cities and in metropolitan areas, especially in the states of São Paulo and Rio de Janeiro, as well as in some states in the Amazon region.

One of the main TB-related comorbidities is HIV infection. In 2005, the incidence of HIV infection in Brazil was 20.7/100,000 population. Consequently, the rate of TB/HIV coinfection is 14% in Brazil and 13% in the state of São Paulo.

In Brazil, the greatest number of TB cases (20%) is found in the state of São Paulo, and information about the epidemiological profile of the various clinical expressions of the disease is scarce. Chief among the extrapulmonary forms, which account for 15% of the total number of cases in Brazil, is pleural TB. However, in the presence of TB/HIV coinfection, the proportion of extrapulmonary cases reaches 20%. Pleural TB is historically considered a primary manifestation resulting from hematogenous or lymphatic dissemination from a pulmonary focus (first infection). The secondary form, which occurs years after the first infection, is considered consequence of the reactivation of pulmonary foci contaminating the pleural space.

The diagnosis of pleural TB is mainly based on the identification of Mycobacterium tuberculosis in the pleural fluid culture or pleural tissue culture. However, new methods show evidence that will allow the replacement of histological analysis or bacteriological analysis. Chief among those new methods are the determination of adenosine deaminase levels, the determination of interferon-gamma levels, nucleic acid sequence-based amplification and the determination of antibody levels.

Since there are no epidemiological studies evaluating pleural TB in Brazil, we believe that the analysis of the cases in the state of São Paulo (from 1998 to 2005) could be useful for national application.

Methods

This was a retrospective, observational, descriptive study carried out in the Pulmonology Section of the Department of Cardiorespiratory Diseases of the University of São Paulo School of Medicine and at the Center for Epidemiological Surveillance of the São Paulo State Department of Health. The study project was approved by the ethics committees of the two institutions involved.

Data reported between 1998 and 2005 were compiled from the Epidemiological Surveillance Tuberculosis System (Epi-TB database) of the São Paulo State Department of Health in February of 2007. Demographic data were obtained from the Brazilian Institute of Geography and Statistics (the 2000 census). After the registries were searched, the incidence was analyzed (number of new cases per 100,000 population).

The total number of TB cases was analyzed. The pulmonary form was individualized, as were the pleural and pleuropulmonary forms among the extrapulmonary forms. Of the criteria listed in the database, the following were considered necessary for making a diagnosis of pleural TB: pleural fluid or pleural tissue positivity for acid-fast bacilli (AFB); positive pleural fluid or pleural tissue culture for Mycobacterium tuberculosis; or histological analysis of the pleura revealing a chronic granulomatous process, with or without caseous necrosis. Patients were defined as having pleuropulmonary TB when, in addition to meeting one of those criteria, they presented sputum positivity for AFB or a positive sputum culture for Mycobacterium tuberculosis.

The diagnostic methods not listed in the database were labeled as “other methods”. These methods included clinical, epidemiological and radiological criteria; pleural fluid analysis (biochemical analysis, determination of adenosine deaminase levels and cytology); and molecular biology studies.

The extrapulmonary forms were analyzed for gender, age bracket, comorbidities (particularly TB/HIV coinfection, alcoholism, diabetes and mental illness) and the period of latency between symptom onset and treatment initiation.

The statistical analysis was performed using the Epi Info program for Windows 2006, and the
level of significance was set at $p < 0.05$. Linear regression analysis was used to evaluate the incidence trend, and analysis of variance was used to compare the incidence coefficients in terms of age bracket and gender.

Results

Between 1998 and 2005, a total of 144,347 new cases of TB were reported in the state of São Paulo. In this eight-year period, the incidence trend suffered a decline (49.7, 50.3, 50.4, 48.3, 47.7, 46.0, 45.0 and 44.6%, respectively; $R^2 = 0.898$; $p < 0.001$). The pulmonary form predominated (118,575 cases; 82.2%), and, among the extrapulmonary forms (25,773 cases; 17.8%), pleural TB was the form most often reported (12,545 cases; 48.7%). The incidence of pleural TB did not vary significantly (4.1, 4.3, 4.8, 4.1, 4.2, 4.0, 4.1 and 3.8%, respectively, from 1998 to 2005; $R^2 = 0.433$; $p = 0.076$; Figure 1).

The diagnosis of (pleural or pleuropulmonary) TB was based on bacteriological methods in 1,780 (14.2%) of the cases. The presence of AFB was confirmed in 1,074 cases (sputum: in 702; pleural fluid: in 372), which accounts for 60.3% of the cases diagnosed bacteriologically and to 8.6% of all cases reported in the period. Sputum, pleural tissue or pleural fluid culture allowed the identification of $M. tuberculosis$ in 706 cases, which accounts for 39.7% of the cases diagnosed bacteriologically and for 5.6% of all cases reported in the period.

Histology of the parietal pleura, revealing a chronic granulomatous process (with or without caseous necrosis), was reported in 3,787 (30.2%) of the cases. In 6,978 (55.6%), the diagnostic method was not reported, being classified as “other methods” (Table 1).

Specific analysis of the pleural form revealed that the lowest incidence coefficients were observed in the under-15-year age bracket, being the same for males and females ($p = 0.364$). Above this age bracket, there was a predominance of males (2:1). The highest incidence coefficients occurred in females aged from 20 to 29 years and in males aged from 30 to 59 years (Figure 2).

Of the total number of patients with pleural TB, 2,028 (16.0%) presented concomitant disease in other locations, the association with pulmonary TB (1,988 cases; 98.0%) being the most common, followed by the association with lymph node, meningeal, renal and ocular TB.

A total of 4,018 (32.0%) of the patients with pleural TB presented comorbidities: alcoholism (1,198; 9.5%); HIV infection (1,001; 8.0%); diabetes (412; 3.3%); and mental illness (147; 1.2%). In 1,260 (10.0%) of the cases, the comorbidity was not specified in the database.

There was a trend toward a reduction in the number of cases of TB/HIV coinfection (12.8, 11.6, 10.1, 7.3, 9.6, 7.9, 7.8 and 8.9%, respectively, from 1998 to 2005; $R^2 = 0.582$; $p < 0.001$). It is of note that, in this period, HIV testing became more widely used, which is confirmed by the increase in the number of negative cases (41.4, 43.9, 50.6, 51.2, 53.8, 59.0, 59.3 and 60.0%, respectively, from 1998 to 2005; $R^2 = 0.936$; $p < 0.001$) and the decrease in the number of cases in which there is no reference to HIV testing (45.9, 45.4, 39.3, 41.6, 36.5,
of TB decreased in the period analyzed, the incidence of the extrapulmonary forms, chief among which is pleural TB, remained stable. Finally, we found that the percentage of extrapulmonary forms reported in the state of São Paulo (18.0%) is higher than that reported in all of Brazil (14.0%).

It is noteworthy that, in countries where there was a reduction in the incidence of TB, the reduction in the incidence of the extrapulmonary forms was found to be less pronounced. This fact was also observed in the state of São Paulo, possibly due to multifactorial causes, such as the improvement of diagnostic techniques and the significant number of cases of reactivation. Another factor to be considered is the usual relationship between reactivation and comorbidities, which are present in 32.0% of the patients with pleural TB. Chief among the comorbidities are

33.0, 32.8 and 31.1%, respectively, from 1998 to 2005; $R^2 = 0.924; p < 0.001$; Figure 3).

Latency between symptom onset and TB diagnosis was reported in 9,408 (75.0%) of the cases. Periods of less than 1 month were reported in 30.0% of those cases, periods of 1 to 2 months were reported in 44.0%, periods of 3 to 6 months were reported in 23.0%, and periods of more than 6 months were reported in 3.0%.

**Discussion**

This study represents the first nationwide approach to the epidemiology of pleural TB in the state of São Paulo. We found that the clinical presentation of extrapulmonary TB accounted for 17.8% of the cases, pleural TB being the most common form. We also observed that, although the incidence trend for all forms of TB decreased in the period analyzed, the incidence of the extrapulmonary forms, chief among which is pleural TB, remained stable. Finally, we found that the percentage of extrapulmonary forms reported in the state of São Paulo (18.0%) is higher than that reported in all of Brazil (14.0%).

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alcoholism (9.5%), HIV infection (8.0%), diabetes mellitus (3.3%) and mental illness (1.2%). It should be borne in mind that, in the state of São Paulo, it is possible that the implementation of antiretroviral regimens reduced the number of patients presenting TB/HIV coinfection, which explains the decrease in the number of cases of pleural TB/HIV coinfection.\(^{[1,5,6]}\)

Another traditional concept is that pleural TB would be a nontransmissible clinical form. In this context, the investigation of pulmonary involvement is not routinely performed, which leads pleuropulmonary TB to be labeled only as pleural TB. This fact is relevant because, if more accurate diagnostic methods, including imaging tests (tomography), bronchoscopy (bronchoalveolar lavage and biopsy), microbiology (culture) and molecular biology tests (PCR) were used, there would be concomitant pleural and pulmonary involvement in 50-80% of patients.\(^{[19,20]}\)

It should be noted that, despite there being no reference to the use of these methods in a systematic way, the pleuropulmonary form was reported in 18.0% of the patients with pleural effusion.\(^{[21,23]}\)

The distribution of pleural TB by anthropometric characteristics reflects the pattern of the disease in its pulmonary presentation,\(^{[16]}\) the male coefficient being twice as high as the female coefficient. Regarding age, it is known that TB, especially in areas of high prevalence, is related to young age brackets, which justifies the inclusion of being younger than 40 years among the diagnostic predictors.\(^{[21]}\) However, a study of pleural TB conducted in Brazil revealed that age presents low sensitivity (73%) and low specificity (46%).\(^{[22]}\) In the present investigation, the highest incidence was found to occur between 30 and 59 years of age, there being a slight decline over 60 years of age. These data are significant because they emphasize that the diagnosis of pleural effusion secondary to TB should be considered regardless of the age of the patient.\(^{[22,23]}\) This fact was also reported in the United States (1993-2003), there being a higher percentage of cases of pleural TB in patients older than 65 years (probable reactivation of a previous infection).\(^{[18]}\)

Regarding the diagnostic criteria for pleural TB in the state of São Paulo, the limitation of this study refers to the analysis of cases reported with unspecified criteria (55.6%), which allows the assumption that diagnoses were based only on clinical-epidemiological or radiological criteria, biochemical criteria and cytological criteria. The analysis of the use of these parameters and mainly of the determination of adenosine deaminase levels is found to be affected in this study, since the reporting forms lacked these data. In countries with a high incidence of TB, the association of epidemiological history, biochemical analysis (an increase in proteins), cytology (lymphocytes/neutrophils > 0.75) and especially the determination of adenosine deaminase levels in the pleural fluid (> 40 U/L) has high sensitivity and specificity for the diagnosis of the disease.\(^{[21-23]}\)

The analysis of the cases in which the criterion considered the gold standard for the diagnosis (bacteriology and histology of the pleura) was used (44.4% of all reported cases) revealed that, in approximately 14.2%, the diagnosis was confirmed through bacteriology—sputum testing positive for AFB (in 5.6%), pleural fluid or tissue testing positive for AFB (in 3.0%) and a positive culture for \textit{M. tuberculosis} (in 5.6%)—and the diagnosis was confirmed through histology in only 30.2%.

In controlled studies evaluating diagnostic methods for pleural TB, biopsy of the parietal pleura revealing a chronic granulomatous process (with or without caseous necrosis) had a sensitivity between 50% and 97%.\(^{[6,12]}\) In the present study, we observed that, according to the Epi-TB database, pleural biopsy was not the diagnostic method most commonly used in the state of São Paulo in the last eight years. This fact allows us to consider the possibility that patients have limited access to specialized clinics capable of performing these procedures.
It is of interest that, although pleural TB is characterized as an acute disease, the period between symptom onset and diagnostic confirmation was found to be long. The time elapsed was shorter than 1 month only in approximately 30% of the cases, ranging from 1 to 2 months in 45%. However, it is a source of concern that, in 22% of the reported cases, the time elapsed ranged from 3 to 6 months, and, in approximately 3%, it was longer than 6 months. The limited access to health care facilities with resources to assess the pleural space adequately can explain this delay.

In the state of São Paulo, the determination of adenosine deaminase levels is not available in the public health care system, being performed only in referral hospitals and in some university centers. The results shown in the present study allow us to propose that biochemical and cytological analysis, as well as the determination of adenosine deaminase levels in the pleural fluid, be performed in the public health care system. Adenosine deaminase, in particular, can be easily evaluated in the public health care system, since this enzyme does not present significant alterations for up to 28 days, after the pleural fluid is centrifuged and stored in a standard domestic refrigerator (4°C). In addition, it is important to emphasize the low cost of the determination of adenosine deaminase levels.[24]

In the absence of a bacteriological or a histological criterion, the diagnosis is registered only as “other forms of diagnosis” in the Epi-TB database of the state of São Paulo. This fact limits the study. However, we believe that the implementation of a new epidemiological surveillance TB system (Web-TB on the Internet) in the state of São Paulo can correct this problem. We also suggest that information be systematized and detailed, including other diagnostic methods, especially molecular biology studies or biochemical and cytological analyses.

We conclude that extrapulmonary TB is more frequently reported in the state of São Paulo than in other states. Among the extrapulmonary forms, pleural TB is the most common, being frequently associated with pulmonary TB. For the extrapulmonary forms, including pleural TB, the incidence remained stable in the eight-year period (1998-2005), although there was a trend toward a decrease in the incidence of the pulmonary forms. For the diagnosis of pleural TB, histology and bacteriology were not the most commonly reported methods, which suggests that these methods are being underutilized. Finally, we reiterate that TB should be considered in all cases of pleural effusion, regardless of gender or age.

Acknowledgments

The authors would like to thank Sumie Matai de Figueiredo, Laedi Santos and Milena Marques Pagliarelli Acencio for their contribution to data collection and additional calculation.

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